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(71) Applicant *(for all designated States except US)*: **UNIVERSITY COLLEGE DUBLIN, NATIONAL UNIVERSITY OF IRELAND, DUBLIN** [IE/IE]; Belfield, Dublin 4 (IE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KAPNISAKIS, Ioannis** [GR/GR]; Kontopoula Kydonias, GR-73 100 Chania (GR). **HENEGHAN, Conor** [IE/IE]; 41 Saint Columbanus Road, Dundrum, Dublin 14 (IE).

(74) Agent: **MACLACHLAN & DONALDSON**; 47 Merrion Square, Dublin 2 (IE).

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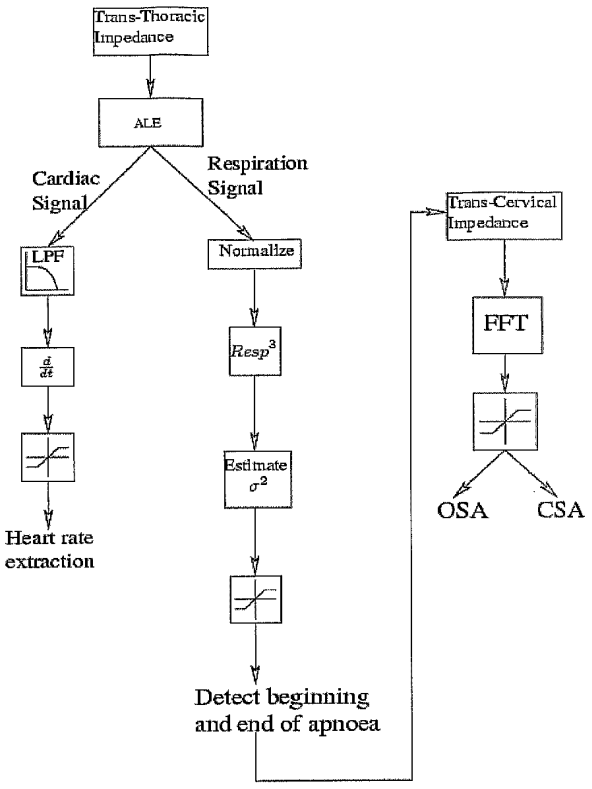

(57) Abstract: A method of detecting sleep apnea using bioimpedance measurements including the steps applying a set of electrodes to a patient to obtain a trans-cervical bioimpedance signal from the patient, over a pre-determined time period; measuring the trans-cervical bioimpedance signal to provide information about respiratory events for that patient over the predetermined time period; estimating the respiration signal using a means for estimating a respiratory signal and using the estimate of respiratory events obtained to detect presence of sleep apnea. An apparatus implementing this method is also provided.

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METHODS AND APPARATUS FOR DETECTING SLEEP APNEA USING BIOIMPEDANCE MEASUREMENTS

The present invention relates to methods for detecting sleep apnea using bioimpedance measurements.

Throughout this specification, electrodes measuring bioimpedance across the neck region of a patient are referred to as the trans-cervical electrodes and electrodes measuring bioimpedance across the torso of a patient are referred to as the trans-thoracic electrodes.

Sleep apnea is commonly defined as the cessation of breathing during sleep. Clinicians usually divide sleep apnea into three major categories – obstructive, central, and mixed sleep apnea. Obstructive sleep apnea (OSA) is characterised by intermittent pauses in breathing during sleep caused by the obstruction and/or collapse of the upper airway. If there is respiratory effort which attempts to maintain airflow, the apnea is considered to be obstructive. OSA is typically accompanied by a reduction in blood oxygen saturation, and leads to wakening from sleep in order to breathe. Central sleep apnea (CSA) is a neurological condition, which causes the loss of all respiratory effort during sleep and is also usually marked by decreases in blood oxygen saturation. Mixed sleep apnea combines components of both CSA and OSA, though treatment of the OSA portion often spontaneously leads to improvement in the CSA condition also. In order for sleep apnea to be considered as clinically significant, the apnea episodes should be of ten seconds or longer duration, and occur more than five times per hour (exact definitions vary from specialist to specialist).

Sleep apnea is conventionally diagnosed using full polysomnography. The signals typically acquired in full polysomnogram include nasal airflow, ribcage and abdominal respiratory effort, electroencephalogram (EEG) recordings, a left and right electrooculogram, and a chin electromyogram.

1. ***Measurements of oro/nasal airflow:*** Oro/nasal airflow can be measured using thermal based devices situated below the nose, in which temperature changes in inspiration and expiration are recorded. An example of such a device is shown in Figure 1. Airflow

can also be measured using air pressure measurement with a nasal prong. Patent publications include US 6,422,240, which discloses an Oral/Nasal Cannula; US 4,648,407, which discloses a method for detecting and differentiating central and obstructive apneas in newborns; and US 6,155,986, which discloses a method of monitoring of oro-nasal respiration. Conventional techniques for measuring oro/nasal airflow can be unreliable, cumbersome, and prone to patient dislocation.

2. ***Measurement of ribcage respiratory effort/respiration***. Techniques include optical methods (US 6,445,942) , inductance plethysmography (US 6,142,953), and bioimpedance measurements, (EP 0 765 632, Siemens, "Method and apparatus for respiration monitoring"). Medtronic EP 0 702 977 have patented a device which measures trans-thoracic impedance and uses that to stimulate upper airway musculature. Techniques of measuring respiration using trans-thoracic bioimpedance are well established and known as impedance pneumography (US 3,677,261, American Optical Corp). Commercial products in impedance pneumography include self-balancing impedance pneumograph RESP1 (UFI) and the cardiac-pneumograph from Rochester Medical Group.

3. ***Methods for measuring cardiac events using bioimpedance***. Bioimpedance is used to measure cardiac events, and is disclosed in patent specifications such as US 6,463,326 (Cardiac Pacemakers, "Rate adaptive cardiac rhythm management device using trans-thoracic impedance") who measure trans-thoracic impedance to extract both cardiac and ventilation parameters. An early trans-thoracic bioimpedance monitor is disclosed in US 4,905,705.

Electrical bioimpedance is a representation of the relationship between the flow of electric current through body tissue and applied voltage. The measurement of electrical bioimpedance has attracted increasing interest in recent years for a variety of purposes. An electrical bioimpedance measurement is typically performed by passing a very low amplitude high-frequency alternating current (AC) across a section of tissue. Typical figures for amplitude and frequency of this current are 500μA and 50 kHz respectively. Since the electrical conductivity of fatty tissue, bone, blood etc. are quite different, the measured impedance can give information about intra-body structure. For example,

electrical impedance is higher in fatty tissue than in lean tissue, which allows bioimpedance to be used to measure body composition.

Another well-developed application of bioimpedance is its use in measuring cardiac output. In a typical impedance cardiography, measurements are made of trans-thoracic impedance, using a pair of current injecting electrodes, and a separate pair of voltage sensing electrodes. Impedance cardiography relies upon the fact that the current seeks the path of least impedance intra-thoracically, which is the blood filled aorta. As the volume of blood in the aorta changes through the cardiac cycle, these changes are reflected in the measured bioimpedance. Through sophisticated analysis of the impedance cardiogram (ICG), the following cardiac parameters can be obtained: stroke volume/index, cardiac output/index, systemic vascular resistance/index (SVR/SVRI), velocity index (VI), thoracic fluid content (TFC), systolic time ratio (STR), left ventricular ejection time (LVET), pre-ejection period (PEP), left cardiac work/index (LCW/LCWI), and heart rate (and related heart rate variability measures).

Moreover, trans-thoracic bioimpedance measurements can also reflect movement of the ribcage and hence can provide information about respiratory effort. Since it is known that obstructive sleep apnea affects both respiratory effort and cardiac inter-beat intervals, it is reasonable that trans-thoracic impedance measurements have utility in the assessment of obstructive sleep apnea. Applicants have discovered that changes in the patency of the upper airway are reflected in changes in bioimpedance measured trans-cervically and applicants have invented novel methods of detecting sleep apnea using bioimpedance measurements.

The present invention seeks to alleviate the disadvantages associated with the prior art.

In a first aspect, the present invention accordingly provides a diagnostic recording apparatus comprising means for measuring at least one electrical impedance measurement from a human and for generating bioimpedance signals; means for analysing said bioimpedance signals to produce output signals and means for providing diagnostic measures of sleep disordered breathing based on said output signals.

Preferably, the apparatus includes signal processing means for filtering out unwanted interference from the bioimpedance signals and for producing processed bioimpedance signals for inputting to the analysing means.

Conveniently, the apparatus includes means for recording the processed bioimpedance signals

Ideally, the means for analysing said processed bioimpedance signals comprises a computer algorithm performed within said apparatus.

Preferably, the apparatus includes a display interface which allows direct inspection of the analysis results.

Conveniently, the means for analysing said processed bioimpedance signals comprises a computer algorithm performed on an external device, and the apparatus includes means for communicating with said external device.

Ideally, the apparatus includes:

means for acquisition of one or more bioimpedance signals, preferably across the thorax providing trans-thoracic measurements and across the neck region providing trans-cervical measurements;

means for calculating components of the bioimpedance signals which can be ascribed to cardiac activity or to respiratory effort,

means for obtaining measurements from the respiratory effort bioimpedance signal to produce diagnostic measures relating to obstructive and central apneas; and

means for obtaining measurements from the cardiac bioimpedance signal which can provide a diagnostic measure of the impact of sleep disordered breathing on cardiac haemodynamic parameters.

In a second aspect the present invention further provides a method of detecting sleep apnea using bioimpedance measurements including the steps of: -

(A) applying a set of electrodes to a patient to obtain bioimpedance signal from the patient, over a pre-determined time period;

(B) measuring the bioimpedance signal to provide information about respiratory events for that patient over the predetermined time period;

(C) estimating the respiration signal using a means for estimating a respiratory signal;

(D) using the estimate of respiratory events obtained from step (C) to detect presence of sleep apnea.

Ideally, the set of electrodes are applied trans-cervically to the patient so as to obtain a trans-cervical bioimpedence signal from the patient.

Preferably, the means for estimating a respiratory signal comprises applying a set of trans-thoracic electrodes to a patient, to obtain a trans-thoracic bioimpedance signal from that patient, over a pre-determined time period.

Thus, in a preferred embodiment, the present invention provides a method of detecting sleep apnea using bioimpedance measurements including the steps of: -

(a) applying a set of electrodes to a patient to obtain a trans-thoracic bioimpedance signal from a patient, over a pre-determined time period;

(b) applying a set of electrodes to a patient to obtain a trans-cervical bioimpedance signal from the patient, over a pre-determined time period;

(c) measuring the trans-thoracic bioimpedance signal to provide information about respiratory and cardiac events for that patient over the predetermined time period;

(d) measuring the trans-cervical bioimpedance signal to provide information about respiratory events for that patient over the predetermined time period;

(e) carrying out a signal processing step on the trans-thoracic bioimpedance signal to produce an estimate of the respiratory effort, airflow and cardiac output (and hence, heart rate) of the patient over the pre-determined time period;

(f) using the estimate of respiratory events obtained from steps (c) and (d) to detect presence of sleep apnea and preferably, classify the episode according to its type.

As an alternative to estimating the respiration signal using trans-thoracic bioimpedance measurements as described at step (e) above, the means for estimating a respiratory signal may comprise a more direct measure such as rib cage movement measured using inductance plethysmography.

Ideally, the signal-processing step at (e) above, comprises: -

passing the trans-thoracic bioimpedance signal through a filter means to separate the respiration and cardiac signal, thereby obtaining two bioimpedance signals, one being associated substantially with airflow, and the other being associated substantially with heart rate (cardiac output).

Ideally, the signal-processing step at (e) above, comprises: -

identifying periods of reduced respiratory effort from the trans-thoracic bioimpedance signal, and then using the spectral content of the trans-cervical signal to distinguish between central and obstructive events.

This invention uses measurements of electrical bioimpedance in the real-time assessment of sleep apnea. Bioimpedance is measured by injecting high frequency sinusoidal AC

current (with amplitude less than 1 mA) with a pair of current injecting electrodes, and then measuring the magnitude and phase of the sinusoidal voltage induced across sections of the body, using a second set of electrodes called the voltage sensing electrodes.

Thus, in a first embodiment of the method of the present invention, a set of trans-thoracic electrodes measures the trans-thoracic impedance and a second set of trans-cervical electrodes measures bioimpedance across the neck. The trans-thoracic electrodes provide estimates of cardiac activity, respiratory effort, and airflow and the measurement provided by the trans-cervical electrodes reflects information primarily about respiratory effort.

However, since the information about airflow is not directly evident in the signal obtained from the trans-thoracic electrodes, signal processing is required to produce an estimate of the airflow. This signal processing comprises firstly separating respiration and cardiac information using a filter. This may be an adaptive filter, in adaptive line enhancement configuration, which effectively subtracts out the cardiac signal from the trans-thoracic bioimpedance signal, thereby obtaining a residual bioimpedance signal associated substantially only with respiration and by using the difference operator to obtain an estimation of airflow.

Preferably, both trans-cervical and trans-thoracic bioimpedance measurements are made simultaneously and are used to detect the presence of apnea. The trans-thoracic bioimpedance measurement is optimised to provide good respiratory signals with no motion artefacts and good cardiac signals.

Ideally, the respiratory events of an obstructive nature are distinguished from those of a central nature through assessment of the spectral content of the impedance signals over the time periods of interest.

The trans-cervical bioimpedance measurement is optimised to provide good respiratory effort signal. Having obtained the bioimpedance measurements, evidence of apnea can be found by looking for

- Loss or variation in the airflow signal

- Loss or diminution of respiratory effort
- Changes in the cardiac interbeat series

These patterns can be detected by visual inspection, or alternatively by use of automated algorithms. The measurement system of the present invention can be integrated with other signals typically used in sleep apnea diagnosis such as pulse oximetry, electroencephalograms, electrocardiogramns, electromyograms, and electrooculograms.

Thus, the method of the present invention ideally comprises the steps of:

a. acquiring multiple bio-impedance signals from a human over a period of time, preferably, including measurements from a trans-thoracic and trans cervical configuration;

b. filtering the signal to remove electrical interference;

c. applying processing to derive two or more signals, which present independent information about respiratory-related activity and cardiac- related activity;

d. obtaining an impedance cardiogram signal from the cardiac-related bioimpedance signal;

e. obtaining an airflow signal from processing of the respiratory-related bioimpedance signal;

f. obtaining a measure of respiratory effort from the respiratory-related bioimpedance signal;

g. joint processing of the signals mentioned in steps c,d,e, and f to identify periods of obstructive and central apnea and hypopnea;

h. characterizing of the results of the processing in step g in terms of clinically accepted measures such as apnea-hypopnea index;

i. processing of the signal obtained in step d to estimate hemodynamic parameters including stroke volume, cardiac output/index, systemic vascular resistance/index (SVR/SVRI), velocity index (VI), thoracic fluid content (TFC), systolic time ratio (STR), left ventricular ejection time (LVET), pre-ejection period (PEP), left cardiac work/index (LCW/LCWI), and heart rate; and

j. processing of the sequence of inter-beat times derived in step (i) in order to assess cyclic variations in heart rate known to be associated with sleep disordered breathing

The method of the invention will now be described more particularly, by way of example only, with reference to the accompanying drawings and in the Example.

In the drawings:

Figure 1 is a photograph of an oro/nasal airflow cannula of the prior art shown positioned under a patient's nose;

Figure 2 is a schematic diagram showing the position of the trans-thoracic electrodes and the trans-cervical electrodes on a patient in accordance with one embodiment of the method of the present invention;

Figure 3 is a graphical representation showing raw signals obtained from trans-thoracic impedance magnitude, trans-cervical impedance magnitude, ribcage respiratory effort, abdominal rib cage effort, and oro/nasal pressure;

Figure 4(a) is a graphical representation showing the measured trans-thoracic raw bioimpedance magnitude (Ω) over a period of 65 seconds;

Figure 4(b) is a graphical representation showing the derivative of the raw bioimpedance signal over the same time period. The peaks in the signal ("E-points") were obtained using a simple threshold technique, and are marked with an x;

Figure 4(c) is a graphical representation showing estimated instantaneous heart rate over the same time period using the measured E points from Figure 5(b). Instantaneous heart rate is obtained by simply taking 1/EE, where EE is the time between adjacent E points.

Figure 5(a) is a graphical representation showing the derivative of the trans-thoracic bioimpedance signal over a period of approximately 90 seconds [d(ICG)/ d t]. The peaks in the signal ("B-points") were obtained using a simple threshold technique, and are marked with an x. Some manual scoring was also necessary to remove spurious peaks;

Figure 5(b) is a graphical representation showing estimated instantaneous heart rate over the same time period using the measured E points from Figure 6(a). Instantaneous heart rate is obtained by simply taking 1/EE, where EE is the time between adjacent E points;

Figure 5(c) is a graphical representation showing corresponding nasal airflow over the same time period. The patient experienced two apneic episodes over this time period. It can be seen that the apnea leads to characteristic bradycardia/tachycardia patterns.

Figure 6 is a block diagram showing the Adaptive Line Enhancement (ALE) technique.

Figure 7(a) is a graphical representation showing the estimated airflow signal over a period of 200 seconds. The signal is closely correlated with the measured airflow.

Figure 7(b) is a graphical representation showing the measured airflow signal using a nasal prong over the same period as Figure 7(a).

Figure 8 displays a block diagram of the automated apnea detection scheme.

Figure 9 displays a block diagram of the peak detector used to obtain the E peaks of the cardiac signal.

EXAMPLE 1

In the first embodiment of the invention, two sets of bioimpedance measurements (trans-thoracic and trans-cervical) were made using an Electrical Bioimpedance Amplifier. This amplifier measures bioimpedance by using a 100μA sinusoidal current at one of four frequencies (12.5, 25, 50 or 100 kHz). Figure 2 shows the location of the electrodes on a patient. The current is injected into the measurement tissue volume using a pair of current electrodes, labelled $I_{in}+$ and $I_{in}-$ as shown in Figure 2. The corresponding AC voltage caused by this current can be measured at the body surface using the voltage sensing electrodes. More robust measurements can be achieved by injecting an equal in-phase current of 50 μA at two locations. The bioimpedance amplifier can also average the differential voltage sensed across two different paths. The bioimpedance amplifier detects the magnitude and phase of the sinusoidal current at the frequency of interest. The trans-thoracic measurements were carried out using a 25kHz current and the trans-cervical measurements were carried out using a 100 kHz current.

The described components of the system provide four electrical signals:

- Magnitude of trans-thoracic bioimpedance
- Phase of trans-thoracic bioimpedance
- Magnitude of trans-cervical bioimpedance
- Phase of trans-cervical bioimpedance

In practice, the magnitude and phase information is closely correlated so that magnitude information only, is processed. Henceforth, in this Example, the trans-thoracic

bioimpedance magnitude is referred to as the trans-thoracic bioimpedance signal, and the trans-cervical bioimpedance magnitude is referred to as the trans-cervical bioimpedance signal.

Figure 3 shows examples of typical raw impedance magnitude signals measured from human volunteers with sleep apnea. It also shows respiratory effort at the ribcage and abdomen, as well as oro/nasal airflow, measured by nasal prong. An important limitation of the prior art, is that measuring respiratory effort alone is insufficient to identify obstructive sleep apnea, as the phenomenon of paradoxical breathing is often seen, in which both ribcage and abdominal effort is present, but no airflow occurs due to an obstructed upper airway.

Signal processing of the measured bioimpedance signals provides means to obtain useful information about the presence of obstructive or central apnea events. The following notation will be used to describe the measured signals:

- Trans-thoracic bioimpedance magnitude $Z[n]$
- Trans-cervical bioimpedance magnitude $N[n]$

Estimated cardiac activity from the trans-thoracic bioimpedance magnitude signal will firstly be presented. One estimate of cardiac activity can be obtained from $Z[n]$ alone. Figure 4a shows measurements of trans-thoracic impedance magnitude over a time period of approximately one minute. This raw signal does not convey much visually useful information; however, the derivative of the signal (Figure 4b) clearly shows the time of left ventricle ejection, as described in the previous section. The corresponding instantaneous heart rate (in beats per minute) is shown. Figure 5 shows the cardiac activity as assessed by this technique during an episode of apnea, interspersed with breathing. Characteristic patterns can be seen in the heart rate, which themselves can be used to assess for apnea.

A more refined signal processing technique will now be described which provides both cardiac, respiratory and airflow information from the trans-thoracic bioimpedance signal $Z[n]$. The trans-thoracic bioimpedance signal $Z[n]$ consists of a slowly-varying almost-

periodic signal that represents a respiratory effort signal $a[n]$ which typically has low harmonic content and is concentrated in a narrow low-frequency band (typically 0.15-0.4 Hz for adult humans). The trans-thoracic bioimpedance also contains an approximate wide-band signal $c[n]$, that represents the cardiac signal. The spectral content of the cardiac signal typically extends from around 1 Hz (which is the fundamental frequency) to several Hz (the harmonics of the fundamental cardiac frequencies). Therefore the trans-thoracic bioimpedance signal can be modeled as a mixture of a periodic (respiration) and wideband (cardiac) signal. A well-known way to separate a periodic and a broadband signal is a special configuration of an adaptive noise canceller termed Adaptive Line Enhancement (ALE).

In general, an adaptive noise canceller attempts to "subtract" out the effect of the signal in a reference input $u[n]$ from the signal in a primary input $d[n]$. The primary input is taken to consist of two signals, which are uncorrelated with each other, and the reference signal consists of a signal that is somehow correlated with one of the signals in the primary input. Mathematically, we can write $d[n] = w[n] + v[n]$, where $w[n]$ is correlated with $u[n]$, and $v[n]$ is uncorrelated with $w[n]$. To separate $w[n]$ and $v[n]$, $u[n]$ is passed through a digital filter $h[n]$ which produces an output $y[n]$ which attempts to identify the component of $d[n]$ dependent on $u[n]$. A residual signal $e[n]$ can then be formed as ($d[n]$-$y[n]$). This residual signal $e[n]$ will then be an estimate of the signal $v[n]$ which is uncorrelated in the two inputs and the output of the filter $y[n]$ will be an estimate of the common signal $w[n]$. To identify the digital filter $h[n]$, a technique called adaptive filtering is used. An adaptive filter outputs a signal $y[n]$ as follows:

$$y[n] = \sum_{k=0}^{L-1} h[k]u[n-k]$$

where L is the length of the filter. The adaptive algorithm attempts to recursively find an optimum filter, which minimises an error signal as follows. The optimum choice of filter coefficients minimises the mean square error between the primary input signal d[n] and the estimated $y[n]$, i.e., h_{opt} *is found* such that $E\left[(d[n]-y[n])^2\right]$ is minimised. In this notation, E[ ] denotes the expectation operator. These optimum filter coefficients can be recursively calculated using a Least Mean Squares (LMS) gradient descent algorithm. In

this algorithm, the set of coefficients at time n+1 is updated from the set at time n, using the relation:

$$h_{n+1}[k] = h_n[k] + \mu e[n]u[n-k] \quad for \quad k = 0,1,\mathrm{K}\ ,L-1$$

where μ is a stepsize parameter, and $e[n] = d[n] - y[n]$. For a suitable choice of μ, the filter coefficients will quickly assume values in and around their optimum values. The resultant signal $e[n]$ will then contain information which is not common to the two signals.

A modification of the general adaptive noise canceller can be used in order to cancel a periodic interference from a wide band signal or to detect a narrow-band signal buried in broad-band noise without the use of an external reference input. The technique is called Adaptive Line Enhancement (ALE), and is particularly suited to our application. A typical ALE signal processing system is shown in Figure 6. The underlying idea is that when a signal consists of a periodic $a[n]$ and wide band component $c[n]$, it is possible to detect the periodic component by creating a reference input which is a delayed version of the primary input. The delay should be longer than the correlation time of the wide-band component, which can be estimated *a priori*. Despite the delay, because of the periodicity of the interference, it will still be correlated in the two inputs and it will appear in the filter output $y[n]$. In the method of the invention, the resultant signal $e[n]$ will then indicate changes in the trans-thoracic impedance magnitude which are solely due to cardiac changes and $y[n]$ will indicate changes in the trans-thoracic impedance magnitude which are due to respiration. Note that techniques for estimating cardiac activity (i.e., determining heart rate, left ventricle ejection time, and other cardiac parameters) can now be applied to $e[n]$ as described below.

Following the adaptive line enhancement process, we now have a signal $y[n]$ which reflects respiratory and airflow information. An estimate of total oro-nasal airflow can be obtained by applying the differential operator to this signal. Figure 7 shows how this estimate of the airflow is well correlated with the true nasal airflow measured independently.

Following the analysis of the previous sections we now describe a scheme for the automatic detection of sleep apnea based solely on bioimpedance. A schematic

representation of the method is shown in Figure 8. Using the electrode topology of Figure 2, we obtain the trans-thoracic and trans-cervical impedance signals. The trans-thoracic signal is passed through an ALE in order to separate the cardiac and respiration information from the impedance signal. The error output of the ALE contains the cardiac information and the high frequency noise of the impedance signal. To obtain useful cardiac information, we employ the signal processing illustrated in Figure 9. The cardiac signal is passed through a low pass filter to eliminate noise (FIR 64 taps, 3 Hz cut-off frequency). Afterwards, we pass the cardiac signal through a first-order differentiator to obtain the first derivative of the signal. The normalized signal is then passed through a threshold-based peak detector in order to find the positions of the E peaks. The threshold can be calculated based on the root mean square of the signal, as shown in Figure 9. The net outcome of the peak detector is a set of locations in time corresponding to the E peaks (which are the point of maximum cardiac outflow). This provides an estimate of the heart rate. This cardiac signal can also be processed to give information about the cardiac stroke volume.

In parallel to cardiac signal processing, we process the respiration signal $y[n]$. Firstly, we create a sliding window that contains a ten-second segment of data. In order to eliminate the baseline wander the trend (linear fit to data) of the segment is removed. Then the signal segment is normalized by dividing by the standard deviation of the last 60 seconds of the data. The third power of the normalized signal segment is calculated, in order to enhance the difference of the standard deviation during normal breathing and the standard deviation during apnea. For that segment, the standard deviation is estimated. If the standard deviation is below a predefined threshold (in our case, set to 0.6) the window is assumed to contain data that corresponds to apnea. Otherwise the data window is said to contain normal breathing. We then measure the time between two successive normal breathing marks, and if that time is greater than 10 seconds then that segment is assumed to contain an apnea episode.

Having identified a respiratory segment from an apnea episode, we then wish to distinguish central from obstructive apnea episodes. We calculate the Fast Fourier Transform (FFT) of the corresponding segment of the trans-cervical impedance. Using these FFT coefficients, we estimate the ratio of the power in the signals over the frequency range of

0.15 to 0.4 Hz to the power in the signal *not* in the range 0.15 to 0.4Hz. If this ratio is below a threshold (set to –3 dB in the current embodiment) then the episode is classified as central apnea; otherwise it is classified as obstructive apnea. We chose to differentiate the apnea episodes using the spectral content of the trans-cervical impedance because the amplitude of the variation in the respiratory signal during obstructive events is subject-dependent, and estimating the spectral content of the trans-cervical signal has proven more robust.

In conclusion, the method of the invention (using a set of bioimpedance measurements) allows the clinician to assess the presence of sleep apnea though provision of measurements relating to

- Cardiac activity (e.g., heart rate)
- Ribcage respiratory effort
- Airflow estimates
- Identification of apnea epsiodes
- Differentiation of central and obstructive episodes

The method of the invention has the advantage that it uses bioimpedance to identify apnea episodes, and to classify them as obstructive or central in nature. The method of the invention also has the advantage that it provides a new technique for assessing oro-nasal airflow, which is independent of nasal thermistors or pressure measurement. It also allows for use of a single transduction technique (impedance measurements), which can simplify the design of an apnea monitoring system.

It will of course be understood that the present invention is not limited to the specific details herein described which are given by way of example only, and that various alternations and modifications may be made without departing from the scope of the invention as defined in the appended claims.

CLAIMS:

1. A diagnostic recording apparatus comprising:

means for measuring at least one electrical impedance measurement from a human and for generating bioimpedance signals;

means for analysing said bioimpedance signals to produce output signals; and

means for providing diagnostic measures of sleep disordered breathing based on said output signals.

2. An apparatus as claimed in Claim 1, including signal processing means for filtering out unwanted interference from the bioimpedance signals and for producing processed bioimpedance signals for inputting to the analysing means.

3. An apparatus as claimed in Claim 2, including means for recording the processed bioimpedance signals.

4. An apparatus as claimed in Claim 2, wherein the means for analysing said processed bioimpedance signals comprises a computer algorithm performed within said apparatus.

5. An apparatus as claimed in Claim 4, including a display interface which allows direct inspection of the analysis results.

6. An apparatus as claimed in Claim 2, wherein the means for analysing said processed bioimpedance signals comprises a computer algorithm performed on an external device, and the apparatus includes means for communicating with said external device.

7. An apparatus as claimed in Claim 1, wherein the apparatus includes:

means for acquisition of one or more bioimpedance signals, measured preferentially across the thorax providing trans-thoracic measurements and across the neck region providing trans-cervical measurements,

means for calculating components of the bioimpedance signals which can be ascribed to cardiac activity or to respiratory effort,

means for obtaining measurements from the respiratory effort bioimpedance signal to produce diagnostic measures relating to obstructive and central apneas; and

means for obtaining measurements from the cardiac bioimpedance signal which can provide a diagnostic measure of the impact of sleep disordered breathing on cardiac haemodynamic parameters.

8. A method of detecting sleep apnea using bioimpedance measurements including the steps of:

(A) applying a set of electrodes to a patient to obtain a bioimpedance signal from the patient, over a pre-determined time period;
(B) measuring the bioimpedance signal to provide information about respiratory events for that patient over the predetermined time period;
(C) estimating the respiration signal using a means for estimating a respiratory signal;
(D) using the estimate of respiratory events obtained from step (C) to detect presence of sleep apnea.

9. A method as claimed in Claim 8 wherein the set of electrodes are applied trans cervically to the patient so as to obtain a trans-cervical bioimpedance signal from the patient.

10. A method as claimed in Claim 8 or Claim 9, wherein the means for estimating a respiratory signal comprise applying a set of trans-thoracic electrodes to a patient, to

obtain a trans-thoracic bioimpedance signal from the patient, over a pre-determined time period.

11. A method as claimed in any one of Claims 8 to 10, wherein the method of detecting sleep apnea using bioimpedance measurements includes the steps of:

(a) applying a set of electrodes to a patient to obtain a trans-thoracic bioimpedance signal from a patient, over a pre-determined time period;

(b) applying a set of electrodes to a patient to obtain a trans-cervical bioimpedance signal from the patient, over a pre-determined time period;

(c) measuring the trans-thoracic bioimpedance signal to provide information about respiratory and cardiac events for that patient over the predetermined time period;

(d) measuring the trans-cervical bioimpedance signal to provide information about respiratory events for that patient over the predetermined time period;

(e) carrying out a signal processing step on the trans-thoracic bioimpedance signal to produce an estimate of the respiratory effort, airflow and cardiac output and hence, heart rate of the patient over the pre-determined time period; and

(f) using the estimate of respiratory events obtained from steps (c) and (d) to detect presence of sleep apnea.

12. A method as claimed in Claim 11, wherein at step (f), having detected the presence of sleep apnea, the episode of sleep apnea is classified according to its type.

13. A method as claimed in Claim 11, wherein the signal-processing step at (e) above, comprises:

passing the trans-thoracic bioimpedance signal through a filter means to separate the respiration and cardiac signal, thereby obtaining two bioimpedance signals, one being associated substantially with airflow and the other being substantially associated with heart rate.

14. A method as claimed in any one of Claims 11 to 13, wherein the signal-processing step at (e) above, comprises:

identifying periods of reduced respiratory effort from the trans-thoracic bioimpedance signal, and then using the spectral content of the trans-cervical signal to distinguish between central and obstructive events.

15. A method as claimed in any one of Claims 11 to 14, wherein the signal processing steps at step (e) comprises firstly separating respiration and cardiac information using a filter.

16. A method as claimed in Claim 15, wherein the filter is an adaptive filter, in adaptive line enhancement configuration, which effectively subtracts out the cardiac signal from the trans-thoracic bioimpedance signal, thereby obtaining a residual bioimpedance signal associated substantially only with respiration and by using the difference operator to obtain an estimation of airflow.

17. A method as claimed in Claim 1, wherein at step (C) the means for estimating a respiratory signal comprises measuring rib cage movement using inductance plethysmography.

18. A method as claimed in any one of Claims 9 to 16, wherein the set of trans-thoracic electrodes measures the trans-thoracic impedance and the set of trans-cervical electrodes measures bioimpedance across the neck whereby the trans-thoracic electrodes provide estimates of cardiac activity, respiratory effort, and airflow and the measurement provided by the trans-cervical electrodes reflects information primarily about respiratory effort.

19. A method as claimed in Claim 18, wherein both trans-cervical and trans-thoracic bioimpedance measurements are made simultaneously and are used to detect the presence of apnea.

20. A method as claimed in Claim 19, wherein respiratory events of an obstructive nature are distinguished from those of a central nature through assessment of the spectral content of the impedance signals over the time periods of interest.

21. A method as claimed in any one of Claims 9 to 20 wherein the trans-thoracic bioimpedance measurement is optimised to provide good respiratory signals with no motion artefacts and good cardiac signals.

22. A method as claimed in Claim 21, wherein the trans-cervical bioimpedance measurement is optimised to provide good respiratory effort signal.

23. A method as claimed in any one of the preceding claims, wherein having obtained the bioimpedance measurements, evidence of apnea can be detected from at least one of the following patterns:

- Loss or variation in the airflow signal
- Loss or diminution of respiratory effort
- Changes in the cardiac interbeat series

24. A method as claimed in Claim 23, wherein said patterns are detected by visual inspection.

25 A method as claimed in Claim 23 wherein said patterns are detected by use of automated algorithms.

26. A method as claimed in any one of the preceding claims, wherein said method can be integrated with other signals used in sleep apnea diagnosis such as pulse oximetry, electroencephalograms, electrocardiogramns, electromyograms, and electrooculograms.

27. A method as claimed in Claim 1, wherein the method comprises the steps of:

a. acquiring multiple bio-impedance signals from a human over a period of time, preferably, including measurements from a trans-thoracic and trans cervical configuration;

b. filtering the signal to remove electrical interference;

c. applying processing to derive two or more signals, which present independent information about respiratory-related activity and cardiac- related activity;

d. obtaining an impedance cardiogram signal from the cardiac-related bioimpedance signal;

e. obtaining an airflow signal from processing of the respiratory-related bioimpedance signal;

f. obtaining a measure of respiratory effort from the respiratory-related bioimpedance signal;

g. joint processing of the signals mentioned in steps c,d,e, and f to identify periods of obstructive and central apnea and hypopnea;

h. characterizing of the results of the processing in step g in terms of clinically accepted measures such as apnea-hypopnea index;

i. processing of the signal obtained in step d to estimate hemodynamic parameters including stroke volume, cardiac output/index, systemic vascular resistance/index (SVR/SVRI), velocity index (VI), thoracic fluid content (TFC), systolic time ratio (STR), left ventricular ejection time (LVET), pre-ejection period (PEP), left cardiac work/index (LCW/LCWI), and heart rate; and

j. processing of the sequence of inter-beat times derived in step (i) in order to assess cyclic variations in heart rate known to be associated with sleep disordered breathing.

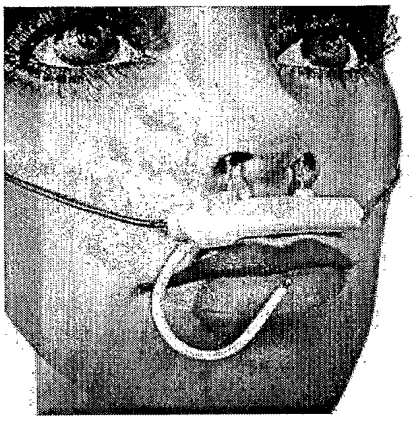

Figure 1 (Prior Art)

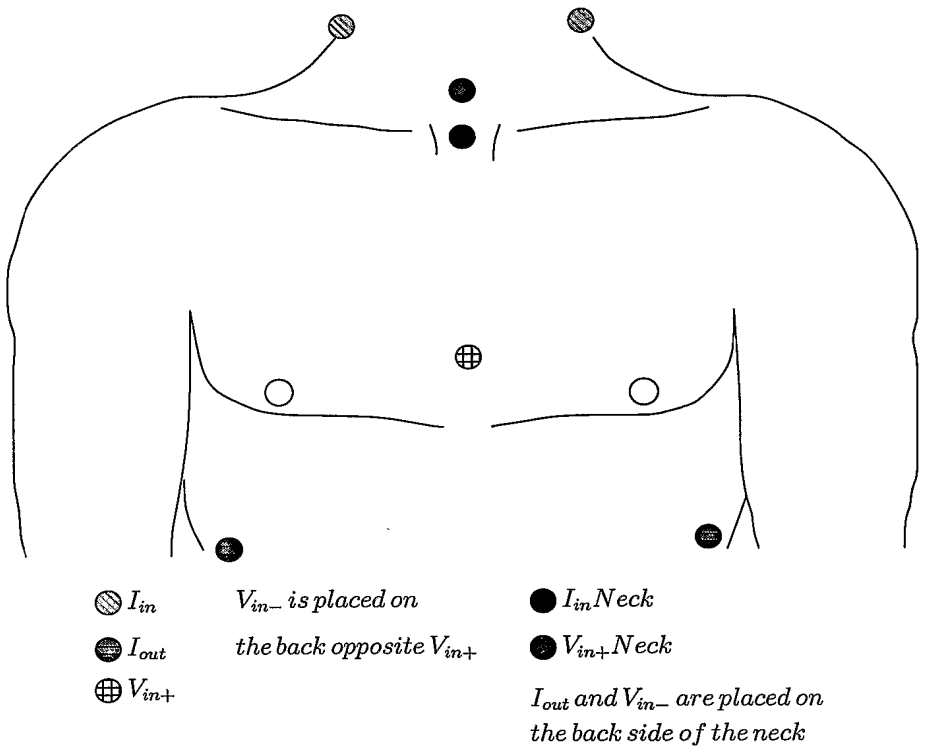
I_{in}
I_{out}
V_{in+}
V_{in-} is placed on the back opposite V_{in+}
I_{in} Neck
V_{in+} Neck
I_{out} and V_{in-} are placed on the back side of the neck

Figure 2

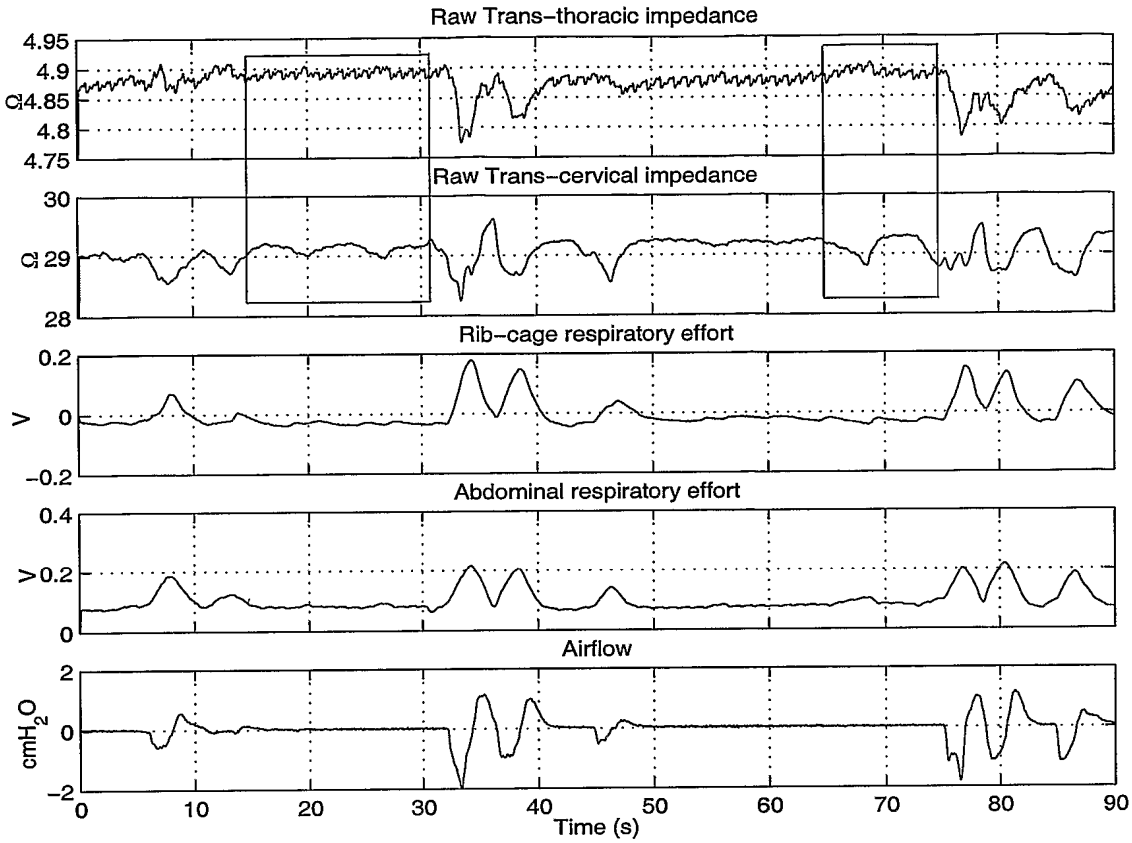
Raw Trans–thoracic impedance
4.95
4.9
4.85
4.8
4.75
Ω
Raw Trans–cervical impedance
30
29
28
Ω
Rib–cage respiratory effort
0.2
0
−0.2
V
Abdominal respiratory effort
0.4
0.2
0
V
Airflow
2
0
−2
cmH2O
0
10
20
30
40
50
60
70
80
90
Time (s)

Figure 3

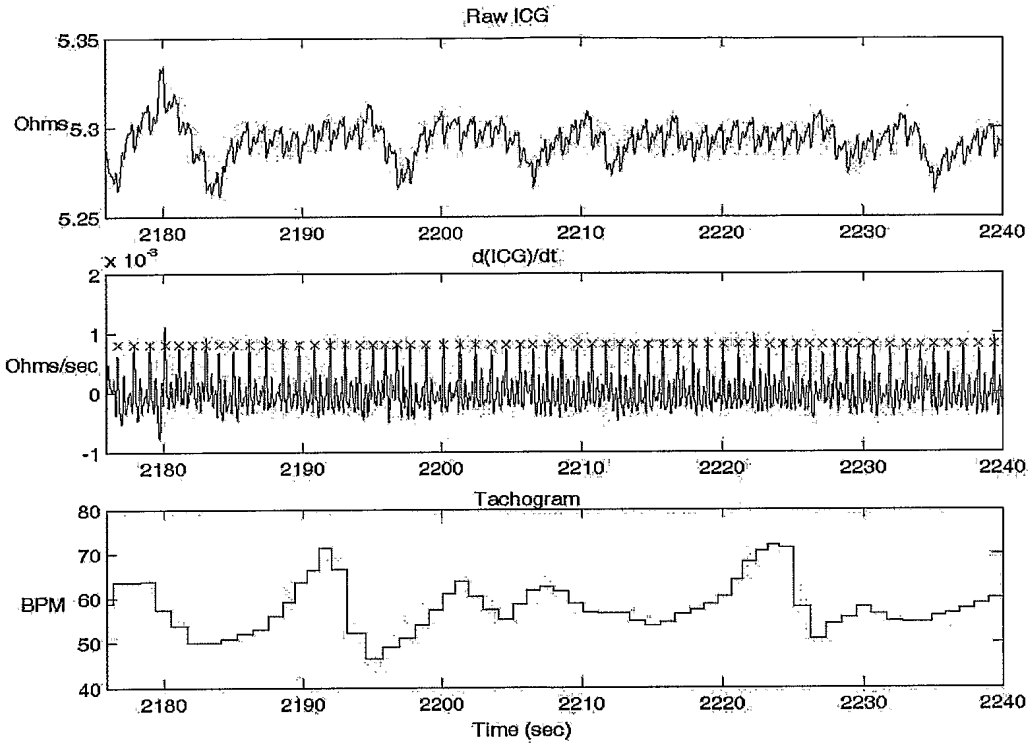

Figure 4(a)

Figure 4(b)

Figure 4(c)

Figure 4

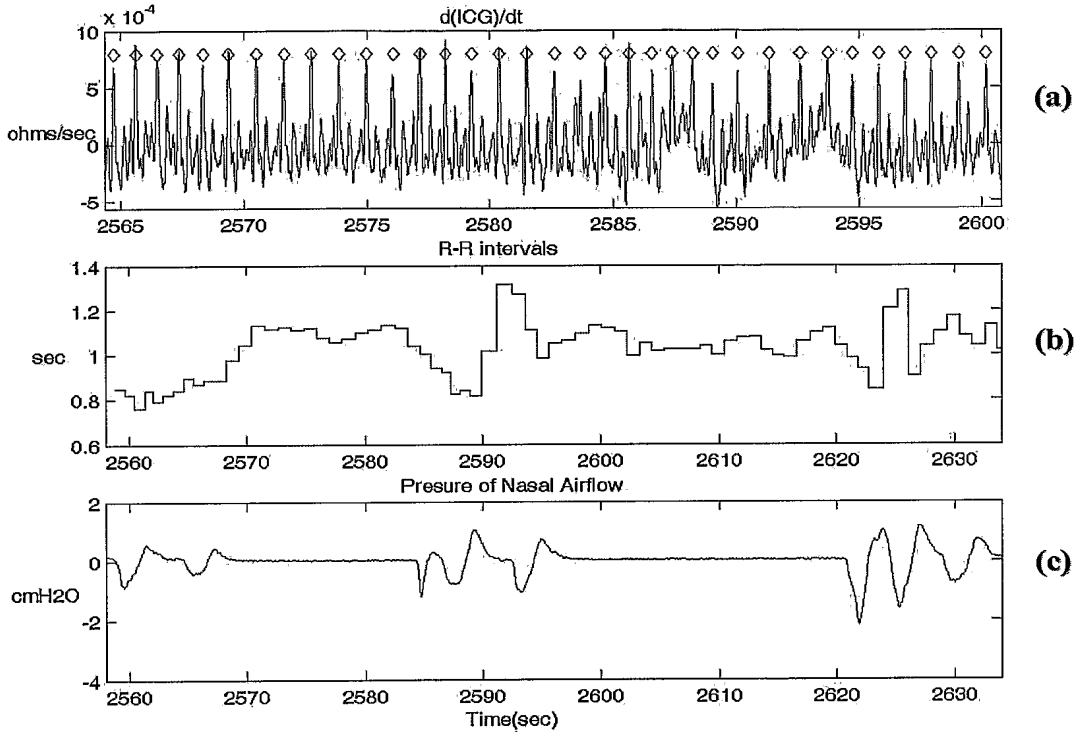
x 10^-4
d(ICG)/dt
10
5
0
-5
ohms/sec
2565
2570
2575
2580
2585
2590
2595
2600
(a)
R-R intervals
1.4
1.2
1
0.8
0.6
sec
2560
2570
2580
2590
2600
2610
2620
2630
(b)
Presure of Nasal Airflow
2
0
-2
-4
cmH2O
2560
2570
2580
2590
2600
2610
2620
2630
Time(sec)
(c)

Figure 5

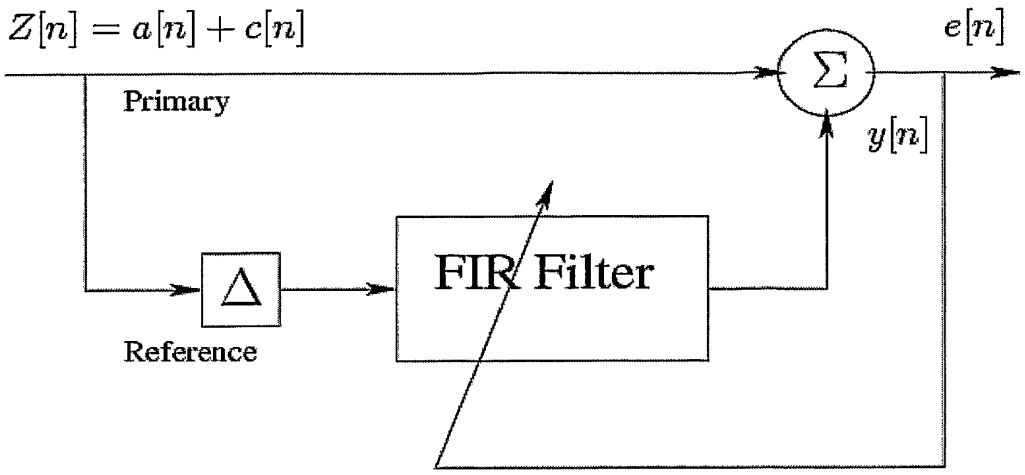

Figure 6

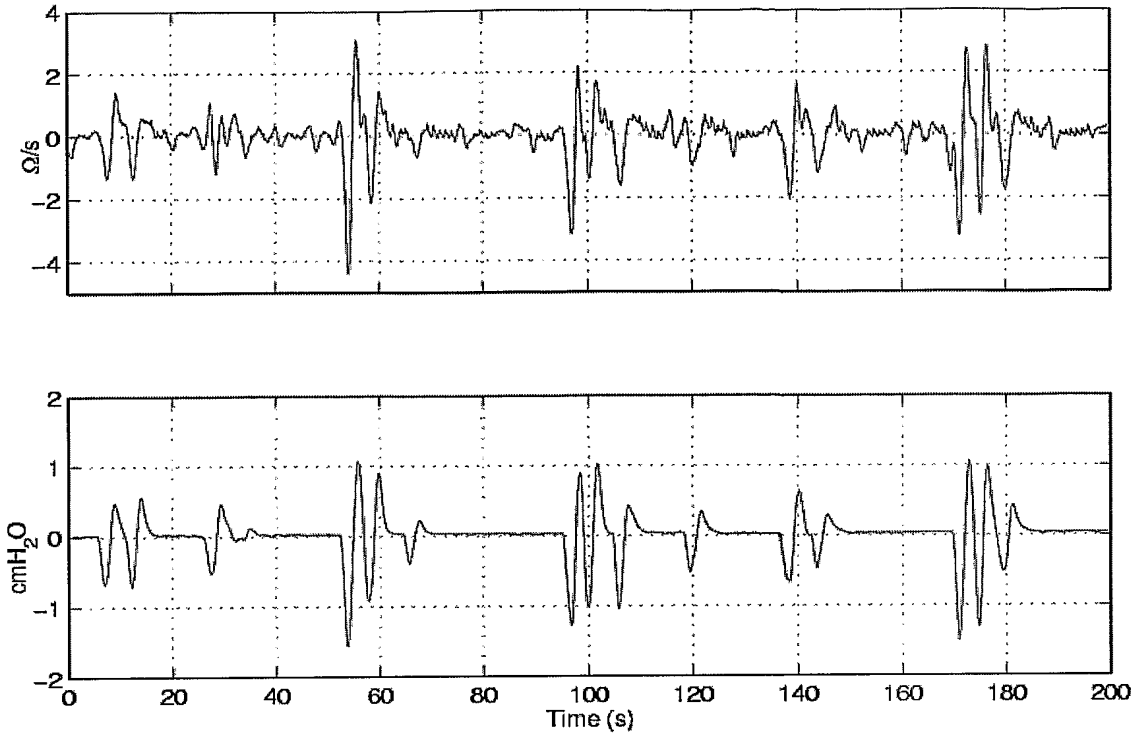

Figure 7

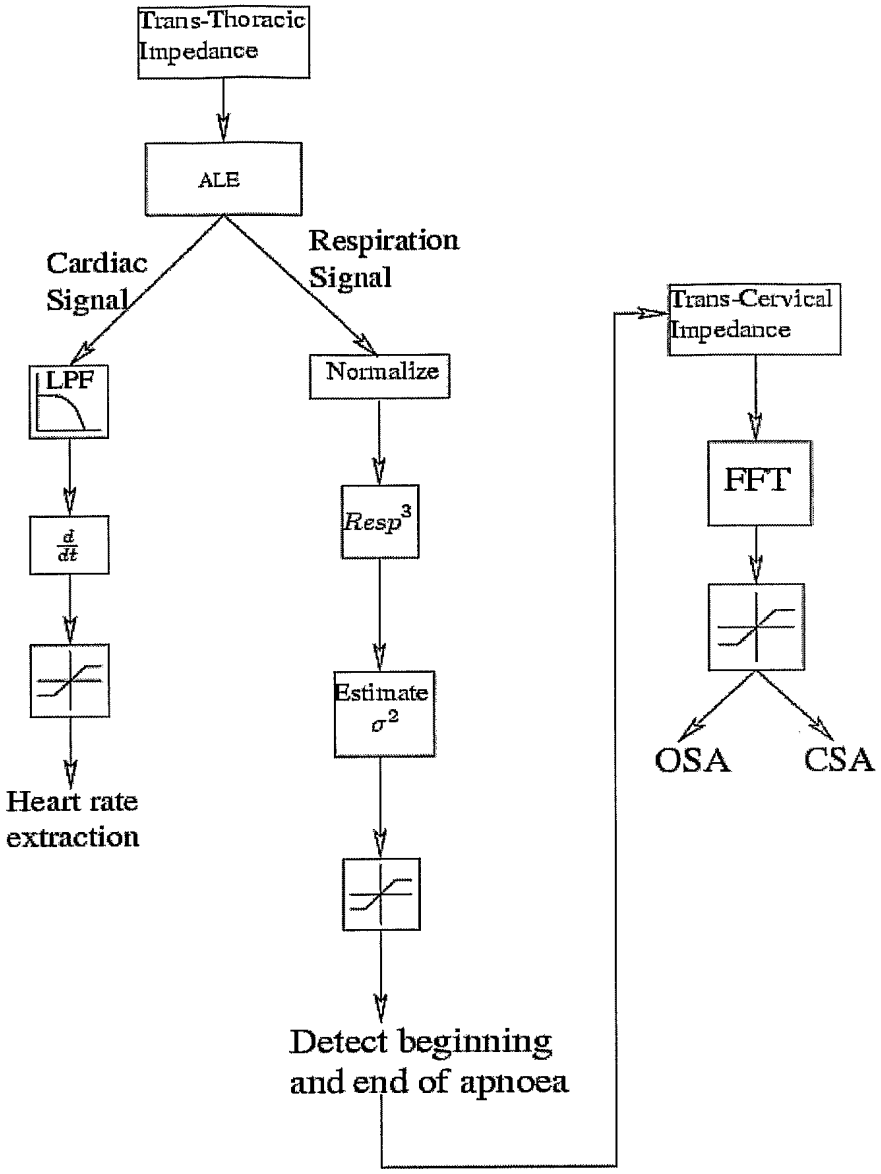
Trans-Thoracic Impedance
ALE
Cardiac Signal
Respiration Signal
LPF
Normalize
$\frac{d}{dt}$
$Resp^3$
Estimate σ^2
Heart rate extraction
Detect beginning and end of apnoea
Trans-Cervical Impedance
FFT
OSA
CSA

Figure 8

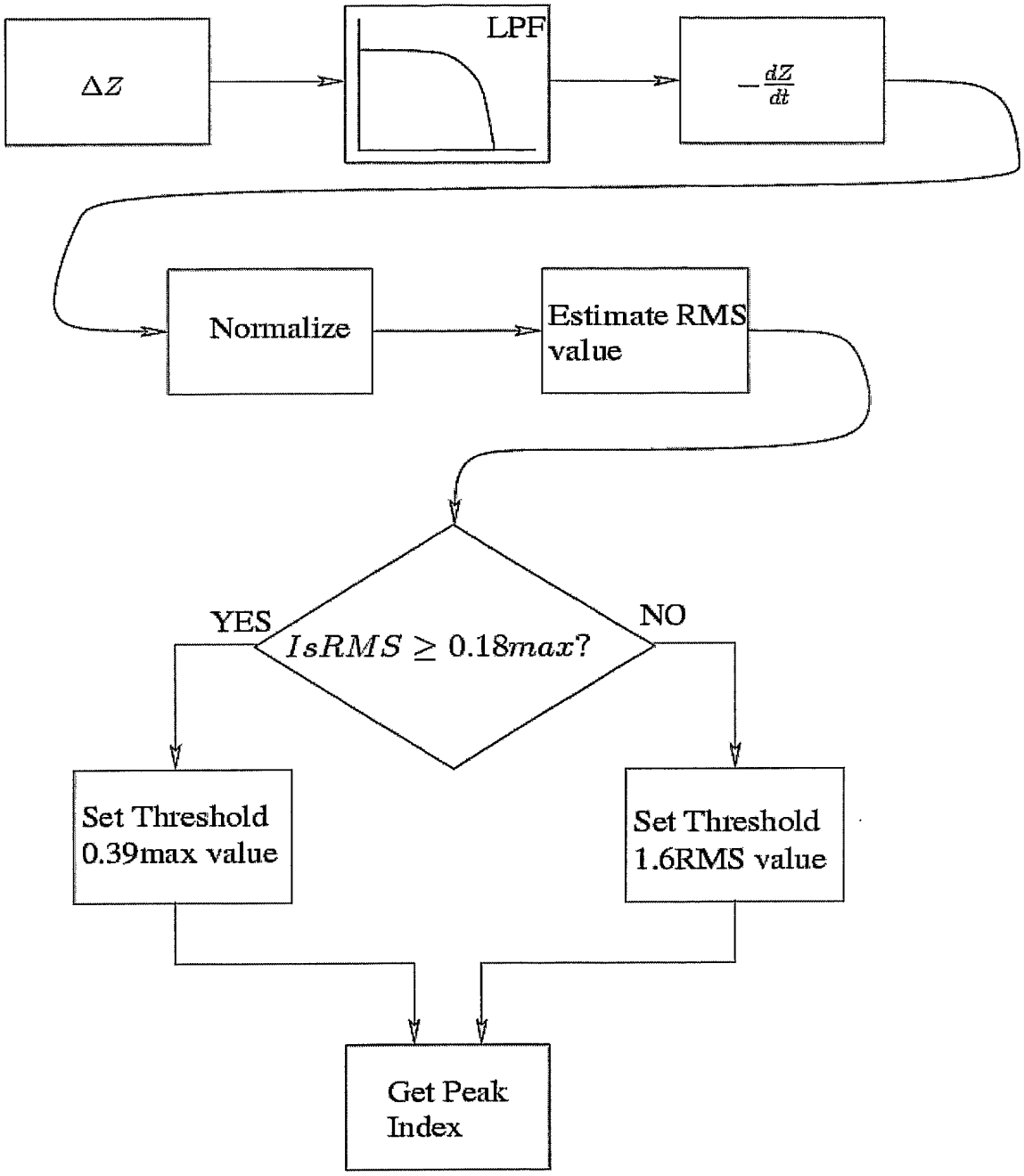
ΔZ
LPF
$-\frac{dZ}{dt}$
Normalize
Estimate RMS value
YES
$IsRMS \geq 0.18max?$
NO
Set Threshold 0.39max value
Set Threshold 1.6RMS value
Get Peak Index

Figure 9

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IE2004/000088

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/053

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 702 977 A (MEDTRONIC INC) 27 March 1996 (1996-03-27) cited in the application column 4, line 53 - column 8, line 6	1-8,10
X	US 6 537 228 B1 (LAMBERT SCOTT) 25 March 2003 (2003-03-25) column 3, line 21 - column 7, line 15	1-5,8,10
X	US 2002/193697 A1 (CHO YONG KYUN ET AL) 19 December 2002 (2002-12-19) paragraphs '0031! - '0047!; figures 3,4	1-4,6-8, 10
X	US 6 015 389 A (BROWN BRIAN HILTON) 18 January 2000 (2000-01-18) column 2, line 1 - column 5, line 34	1,2,8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 2004	04/11/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hooper, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/IE2004/000088

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		EP 1385425 A1	04-02-2004
		JP 2004529707 T	30-09-2004
		WO 02087433 A1	07-11-2002
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		JP 2000517199 T	26-12-2000